

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 November 2003 (06.11.2003)

PCT

(10) International Publication Number
WO 03/090730 A1

(51) International Patent Classification⁷: **A61K 31/00**,
31/415, 31/4178, 31/404, 31/5513, 31/4365, A61P 29/02

(21) International Application Number: PCT/GB02/01902

(22) International Filing Date: 25 April 2002 (25.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **GENERICS [UK] LIMITED** [GB/GB]; Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 1AG (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **NDZIE, Elias** [GB/GB]; Albany Gate, Darkes Lane, Potters Bar, Hertfordshire EN6 1AG (GB).

(74) Agents: **JUMP, Timothy et al.**; Venner, Shipley & Co., 20 Little Britain, London EC1A 7DH (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

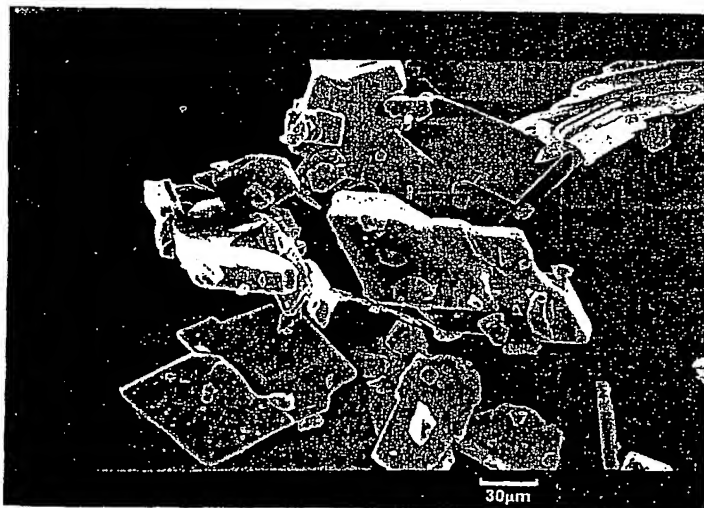
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL CRYSTALLINE FORMS OF CELECOXIB AND OTHER COMPOUNDS

A scanning selection microscope image of the Celecoxib:
DMA adduct prepared in example 1.



(57) Abstract: An organic compound in a solid crystalline form that affords the compound improved handling properties and/or improved properties as a pharmaceutical agent. The compound is preferably in the form of an adduct or solvate with an organic solvent.

BEST AVAILABLE COPY

WO 03/090730 A1

NOVEL CRYSTALLINE FORMS OF CELECOXIB AND OTHER COMPOUNDS

DESCRIPTION

5 The present invention relates to novel crystalline forms of organic compounds, particularly those that are pharmaceutically active, processes for preparing such forms, compositions comprising such forms, and uses for such forms and compositions.

10 The manufacturing process for many pharmaceuticals is hindered by the fact that the organic compound which is the active drug substance has an irregular crystalline form. In some cases, such irregularities can cause handling difficulties during the manufacturing process and these can lead to undesirable properties being imparted
15 to the final drug or dosage form. The latter include inconsistent drug substance dissolution rates and the like.

According to a first aspect of the invention, there is provided an organic compound in a solid crystalline form that affords the compound improved handling properties
20 and/or improved properties as a pharmaceutical agent. Preferably, said crystalline form is particulate and comprises substantially regularly shaped and free flowing crystalline particles that are preferably more free flowing and regular in shape than previously known forms of the compound. The compound is preferably dry and substantially free of water. When substantially free of water, the organic compound
25 preferably includes no more than 5, 2, 1, 0.5% water.

The organic compound is preferably in the form of an adduct with an organic solvent, preferably a polar organic solvent that is preferably miscible with water. The adduct is preferably a solvate, wherein the solvent is bound into the crystal
30 lattice of the organic compound and cannot be removed by conventional vacuum drying, for example, at a vacuum of down to 50, 40, 35, 30, 25 or 20 mm Hg, preferably 30 mm Hg, at a temperature of up to 20, 25, 35, 40, 45, 50, 55, 60°C, preferably 45 °C. The organic solvent can be dipolar and/or aprotic. The organic

compound is preferably soluble in the organic solvent but substantially less soluble or insoluble in water. Organic solvents which form a solvate in accordance with the invention can be identified by routine experimentation. However, the organic solvent is preferably dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA) or 1-methyl-2-pyrrolidone (NMP). A plurality of solvents can be present in the adduct or solvate.

The adduct can comprise any ratio between the organic compound and the organic solvent(s), but it is preferably a 1:1 adduct or solvate, in the sense that it includes a 1:1 ratio of molecules of organic compound to solvent molecules in its crystal structure. The adduct or solvate, preferably, has a crystal structure that includes a regular array of solvent and organic compound molecules.

An example of a drug substance which has an irregular crystalline structure, when prepared by heretofore known techniques, is the selective cyclooxygenase-2 (COX-2) inhibitor 4-(5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide which is more commonly known by its generic name Celecoxib. The irregular crystalline shape of Celecoxib prepared by conventional crystallisation techniques can be seen in the scanning electron microscope image represented by Figure 1.

Thus, in a second aspect, the present invention provides a Celecoxib adduct, comprising Celecoxib and an organic solvent, in a solid crystalline form. The organic solvent is preferably of the type employed in compounds in accordance with the first aspect of the invention and adducts in accordance with the second aspect of the invention, preferably, have the same properties as those set out above for adducts in accordance with the first aspect of the invention.

In a preferred embodiment of the first aspect of the invention, the organic compound is Celecoxib.

Other organic compounds which may be the subject of the present invention are Rofecoxib, Olanzapine, Zafirlukast, Ondansetron, Clopidogrel, Ticlopidine but the

invention can be applied to any organic compound which has an irregular crystalline form. The compound can be in the form of a free base or a pharmaceutically acceptable salt or ester, such as a hydrochloride or like acid addition salt.

5 The inventive crystalline form or adduct is preferably preparable or prepared by a method comprising crystallisation from a solution of the organic compound in the solvent(s), preferably by precipitating said form or adduct from a solution of the organic compound in the organic solvent(s) by the addition of water to the solution. Said method, in an embodiment, also comprises the step of drying the precipitate to
10 provide a crystalline form of the organic compound, or adduct or solvate, in accordance with the invention. The crystalline form, adduct or solvate can be dried under conventional vacuum drying conditions, for example, under a vacuum of down to 50, 40, 35, 30, 25 or 20 mm Hg, preferably 30 mm Hg, at a temperature of up to 20, 25, 35, 40, 45, 50, 55, 60°C, preferably 45 °C.

15

The crystalline forms and adducts in accordance with the invention can be used to advantage in the preparation of pharmaceutical dosage or drug forms. When in particulate form, the crystalline forms and adducts in accordance with the invention are free flowing and do not present any of the handling difficulties associated with
20 irregularly shaped crystals. They, therefore, can be employed in the manufacture of pharmaceuticals that do not suffer from the problems, such as inconsistent drug substance dissolution rates and the like, that can be manifest in dosage forms manufactured using drug substances that have irregularly shaped crystals.

25

Accordingly, in further aspects, the present invention provides a method of preparing a pharmaceutical dosage form that utilises a crystalline form or adduct in accordance with the first or second aspect of the invention. It also provides a pharmaceutical dosage form prepared or preparable by such a method. The dosage form is preferably solid and can comprise a crystalline form or adduct in accordance
30 with the invention, in addition to one or more conventional pharmaceutically acceptable excipient(s). Preferred dosage forms in accordance with the invention include tablets, capsules and the like. Tablets can be prepared by conventional techniques, including direct compression, wet granulation and dry granulation.

Capsules are generally formed from a hard gelatine material and can include a conventionally prepared granulate of excipients and a crystalline form, adduct or solvate in accordance with the invention. The excipients can include lactose, sodium lauryl sulphate, povidone, croscarmellose sodium and magnesium stearate.

5

The adducts or solvates in accordance with the invention can also be used to prepare alternative crystalline forms of the organic compound in accordance with the first aspect of the invention, which alternative forms are substantially free of bound organic solvent. Crystalline forms in accordance with the first aspect of the invention that are substantially free of bound organic solvent include less than the amount of solvent which would remain bound within the crystal lattice of the adduct or solvate under conventional vacuum dried conditions. Typically, this means that the amount of bound organic solvent, on a weight for weight basis, would be less than 2.0%, preferably less than 1.8%, more preferably less than 1.5%, even more preferably less than 1.0%, yet more preferably less than 0.5% and most preferably less than 0.1%. These alternative forms are preferably novel polymorphic forms of the organic compound and they can be prepared by removing the solvent from the adduct, for example, by drying or by the use of a displacing agent, such as water, supercritical carbon dioxide, pyridine or a halogenated solvent. When supercritical carbon dioxide is used the flow rate, temperature and pressure of the carbon dioxide should be controlled to give the optimum solvent removal from the organic compound. Generally, high pressure carbon dioxide may be used for example at about 2500 psi. Elevated temperatures may also be preferably used such as between 50 to 80°C. More preferably between 55 to 75°C.

25

The absence of organic solvent from these alternative forms can be an advantage in certain circumstances. For example, they can be employed in place of adducts or solvates in accordance with the present invention if the conditions required to formulate a particular dosage form would be potentially detrimental to the stability of such an adduct or solvate. Accordingly, the ability of adducts and solvates in accordance with the invention to facilitate the preparation of solvent free entities in accordance with the first aspect of the invention is a significant advantage.

30

The present invention also provides, in a further aspect, a process for preparing a crystalline organic compound wherein the crystalline form affords the compound improved handling properties and/or improved properties as a pharmaceutical agent comprising crystallising the organic compound or an intermediate to the said organic compound from a first organic solvent. The inventive process may provide a crystalline organic compound which is an adduct or solvate with a second organic solvent(s). The first and second organic solvent referred to in the above process may be the same solvent. A co-solvent (or anti-solvent), such as water, may be used in the process to facilitate the crystallisation.

The inventive process preferably comprises precipitating a crystalline form, adduct or solvate in accordance with the invention, from a solution of the organic compound in an organic solvent or mixture of solvents by the addition of water to the solution. Said method, in an embodiment, also comprises the step of drying the precipitate to provide a crystalline form of the organic compound, adduct or solvate, in accordance with the invention. Drying preferably involves conventional vacuum drying, for example, at a vacuum of down to 50, 40, 35, 30, 25 or 20 mm Hg, preferably 30 mm Hg, at a temperature of up to 20, 25, 35, 40, 45, 50, 55, 60°C, preferably 45 °C.

The organic solvent used in processes in accordance with the invention, preferably, is a polar organic solvent that is preferably miscible with water. The organic solvent can be dipolar and/or aprotic. The organic compound is preferably soluble in the organic solvent but substantially less soluble or insoluble in water. Organic solvents which form a solvate in accordance with the invention are preferred and can be identified by routine experimentation. However, the organic solvent is preferably dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA) or 1-methyl-2-pyrrolidone (NMP). A mixture of solvents can also be used.

Celecoxib is a non-steroidal anti-inflammatory drug used for symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis. It is currently available in capsules comprising either 100 mg or 200 mg doses. It is preferred, therefore, that dosages forms in accordance with the present invention, wherein the organic

compound is Celecoxib or a Celecoxib solvent adduct or solvate, should include sufficient of the latter to provide a dose of between 50 mg and 300 mg, preferably 100 mg or 200 mg, of the Celecoxib active agent.

- 5 In a further aspect of the invention, there is provided the use of an organic compound in accordance with the first aspect of the invention, wherein said compound is Celecoxib, for the preparation of a medicament for use in treating osteoarthritis or rheumatoid arthritis.
- 10 The present invention is illustrated but in no way limited by the following examples and figures.

Brief description of Figures

- 15 Figure 1 - A scanning electron microscope image of Celecoxib crystals produced by conventional crystallisation techniques.

Figure 2 - A scanning electron microscope image of the Celecoxib:DMA adduct prepared in example 1.

20

Figure 3 - A scanning electron microscope image of the Celecoxib:DMSO adduct prepared in example 2.

Figure 4 - A scanning electron microscope image of the Celecoxib:NMP adduct prepared in example 3.

25

Figure 5 - A XRPD diagram of the Celecoxib:DMA solvate adduct prepared in example 1

Figure 6 - A XRPD diagram of the Celecoxib:DMSO solvate adduct prepared in example 2

30

Figure 7 - A XRPD diagram of the Celecoxib:NMP solvate adduct prepared in example 3

5 Figure 8 - An IR spectrum of the Celecoxib:DMA solvate adduct prepared in example 1

Figure 9 - An IR spectrum of the Celecoxib:DMSO solvate adduct prepared in example 2

10 Figure 10 - An IR spectrum of the Celecoxib:NMP solvate adduct prepared in example 3

Figure 11 - - A XRPD diagram of Celecoxib crystals produced by conventional crystallisation techniques.

15

Figure 12 - An IR spectrum of Celecoxib crystals produced by conventional crystallisation techniques.

The X-ray diffraction patterns set out herein were obtained using a Siemens D5000
20 X-ray powder diffractometer having a copper K_{α} radiation source of wavelength, $\lambda=1.541\text{\AA}$.

The IR spectra were obtained using a Bruker Equinox 55 Attenuated Total Reflectance (ATR).

25

Reference example

Celecoxib crystals produced by conventional crystallisation techniques

30 See Fig 1

Specific IR absorption bands: 3997, 3329, 3222, 1445, 1344, 1273, 1227, 1128, 980, 903, 844, 790, 760, 618, 560cm^{-1} - see Fig 12

Melting point: 160-164°C

XRPD significant peaks – See Fig 11 and Table 1

Table 1: XRPD data of Celecoxib crystals produced by conventional crystallisation
5 techniques

Two theta (°)	Relative Intensity (I/I ₁) %
5.17	22.9
5.42	30.2
9.0	40.5
9.86	29.1
10.37	19.6
10.77	25.2
11.08	42.9
13.1	30.2
14.91	52.5
15.27	14.2
15.47	13.2
16.18	31.6
17.44	13.1
17.99	92.9
18.5	86.7
18.8	100
19.71	95.9
20.32	10.5
20.57	24.5
21.43	61.8
21.78	21.0
22.19	34.7
22.44	82.3
22.79	14.0

23.35	61.6
23.55	99.8
24.0	8.4
24.66	40.8
25.06	45.5
25.47	77.3
25.77	10.5
26.02	8.0
26.23	6.7
26.38	7.0
27.03	12.0
27.54	11.1
27.79	25.5
28.14	12.5
28.30	26.1
29.56	35.2
29.71	19.7
30.06	42.6
30.37	8.9
30.52	8.6
31.12	7.9
31.53	7.6
32.18	10.0
32.59	5.8
35.11	10.0
35.37	7.2
35.77	15.0
36.07	6.9
36.53	6.5
36.88	5.2
37.39	8.3
37.99	12.8

38.45	9.9
38.75	7.0
39.30	7.3
39.51	7.4

Examples

Example 1 – 1:1 Celecoxib:DMA Adduct

1.35g Celecoxib was dissolved into 6mL of DMA under stirring at 45°C (inner temperature) for 5 to 10 minutes. To the clear solution obtained water was added dropwise under stirring. The temperature of the solution rose to 54 - 55°C and the first crystals appeared after adding less than 2mL of water. The addition of water to the suspension was continued to 25mL under stirring, the temperature was allowed to cool and maintained at 45°C. The above suspension was maintained under stirring for 15 minutes and filtered off. The white solid was dried at 45°C under vacuum (30mm Hg) in an oven for 12 hours. Yield: 1.54g. The product was confirmed to be a 1:1 adduct by NMR.

See Fig 2

Specific IR absorption bands: 3997, 3128, 1604, 1471, 1404, 1342, 1269, 1233, 1127, 1098, 972, 838, 816, and 597cm⁻¹ – See Fig 8

Melting point: 145-149°C

XRPD significant peaks – See Fig 5 and Table 2

Table 2: XRPD data of Celecoxib DMA solvate

Two theta (°)	Relative Intensity (I/I ₁) %
7.64	12.7
8.60	56.4
10.57	8.2

12.44	41.3
12.89	66.4
13.60	9.3
13.95	12.7
15.27	56.3
15.67	70.9
16.07	25.1
16.48	39.5
17.14	37.3
18.04	64.8
18.40	6.9
18.70	5.6
19.05	28.8
19.31	94.8
19.66	100
20.17	29.6
20.32	18.9
20.77	34.6
21.12	68.6
21.58	44.3
21.78	16.8
22.03	5.4
22.54	81.8
22.84	5.9
23.14	52.1
23.50	37.6
24.21	13.5
24.41	12.7
24.66	39.3
24.91	16.6
25.16	12.3
25.27	10.4

25.67	18.6
25.87	43.2
26.17	27.9
26.53	4.5
26.98	5.6
27.29	20.8
27.59	8.6
28.09	8.0
28.65	11.9
29.0	10.3
29.51	17.6
29.86	8.2
30.11	19.1
30.37	12.3
30.72	10.8
30.82	10.3
31.33	5.9
31.58	6.2
31.88	12.7
32.08	11.4
33.04	8.7
33.35	7.9
33.55	7.2
33.90	6.5
34.46	4.5
34.76	3.8
34.96	5.1
35.21	10.9
35.92	6.7
36.17	6.0
36.32	5.1
36.53	6.1

37.03	7.7
37.59	7.0
37.99	3.5
38.29	8.8
38.65	7.2
38.95	7.0
39.20	5.1
39.56	5.0
39.86	8.0

Example 2 - 1:1 Celecoxib:DMSO Adduct

- 5 1.30g of Celecoxib was dissolved into 2mL of DMSO under stirring at 45°C (inner temperature) for 5 to 10 minutes. Water (25ml) was added to the clear solution dropwise. The temperature rose to 48 - 50°C during the addition of the first 2 to 3mL of water and a precipitate appeared. The addition of water to the suspension was continued under stirring while the temperature was maintained at 45°C. The
10 above suspension is kept under stirring after water addition for 15 minutes at 45°C and filtered off. The white solid is dried at 45°C without vacuum for 12 hours. Yield: 1.41g. The product was confirmed to be a 1:1 adduct by NMR.

See Fig 3

- Specific IR absorption bands: 3133, 1594, 1472, 1405, 1342, 1272, 1233, 1126, 1099,
15 1017, 974, 895, 840, 815 and 626cm⁻¹ – See Fig 9

Melting point: 105-110°C

XRPD significant peaks – See Fig 6 and Table 3

Table 3: XRPD data of Celecoxib DMSO solvate

20

Two theta (°)	Relative Intensity (I/I ₁) %
7.44	69.5

8.70	89.3
10.42	64.6
12.69	87.0
13.10	100
13.60	46.7
13.75	43.0
13.90	44.8
14.0	54.5
14.31	45.5
15.12	99.4
15.97	90.7
16.18	52.5
16.93	55.7
17.34	68.4
18.04	79.6
18.50	49.1
18.80	55.3
19.0	33.3
19.16	36.7
19.46	33.9
19.71	79.6
19.96	80.7
20.17	86.3
20.82	77.3
21.12	56.4
21.58	69.7
21.83	35.3
22.24	30.4
22.44	45.8
22.74	43.3
23.35	72.5
23.60	43.3

23.80	47.8
24.10	38.5
24.41	21.3
24.86	57.9
25.06	28.5
25.27	21.4
25.47	30.8
25.87	60.6
26.33	33.7
26.53	26.2
26.88	23.3
26.98	25.5
27.29	27.4
27.79	25.6
28.30	17.8
28.40	18.1
28.50	21.0
28.80	15.5
28.95	16.2
29.10	16.1
29.41	30.7
30.11	21.3
30.21	19.3
30.42	16.6
30.52	16.6
30.77	16.9
31.17	20.0
31.43	19.2
31.98	18.0
32.18	15.8
32.54	16.7
32.74	19.3

33.29	11.6
33.40	12.2
33.75	15.7
33.95	13.6
34.15	12.3
34.30	10.3
34.41	9.8
34.51	11.0
34.61	12.9
34.66	12.9
34.81	11.7
35.06	13.6
35.16	11.6
35.26	10.0
35.37	11.5
35.47	11.8
35.62	11.7
35.97	12.9
36.07	12.0
36.17	12.7
36.27	12.8
36.43	13.0
36.68	10.1
36.93	11.9
37.03	12.6
37.13	11.4
37.23	12.3
37.39	15.6
37.74	10.3
37.84	10.1
37.99	12.5
38.09	12.0

38.24	11.8
38.34	11.6
38.45	11.2
38.70	10.1
38.90	10.7
39.10	9.3
39.20	9.6
39.46	10.9
39.61	11.0
39.71	11.7

Example 3 - 1:1 Celecoxib:NMP Adduct

- 5 0.96g of Celecoxib was dissolved into 4mL of NMP under stirring at 45-60°C (inner temperature) for 5 to 10 minutes. Water (15ml) was added to the clear solution dropwise. A precipitate appears after addition of 5mL of water. The addition of water to the suspension was continued under stirring. The above suspension is kept under stirring after water addition for 15 to 20 minutes and filtered off. The white
10 solid is dried at 45°C under vacuum (30mm Hg) for 12 hours. Yield: 1.12g. The product was confirmed to be a 1:1 adduct by NMR.

See Fig 4

Specific IR absorption bands: 2931, 1680, 1649, 1471, 1402, 1341, 1299, 1234, 1152, 1101, 973, 892, 809, 626, 563cm⁻¹ – See Fig 10

- 15 Melting point: 135-140°C

XRPD significant peaks – See Fig 7 and Table 4

Table 4: XRPD data of Celecoxib NMP solvate

Two theta (°)	Relative Intensity (I/I ₁) %
7.54	21.5
7.74	19.8

7.84	19.1
8.25	24.0
12.24	14.4
12.54	36.2
12.79	35.7
13.50	12.9
13.65	11.6
14.0	18.0
15.06	80.4
15.72	84.1
16.38	27.4
17.99	89.9
18.50	16.2
19.16	35.7
19.56	100
20.06	32.0
20.97	60.7
21.23	52.7
21.63	57.1
21.98	11.9
22.54	67.5
22.84	11.6
23.09	48.5
23.6	23.1
24.76	53.0
25.11	8.9
25.32	8.0
25.62	32.3
25.82	25.3
26.43	8.1
27.03	20.5
27.49	11.3

27.69	6.3
28.55	8.7
29.05	18.9
29.76	10.8
30.06	15.8
30.37	11.6
30.52	8.5
30.92	10.0
31.17	7.1
31.48	5.7
31.93	10.1
32.34	7.5
33.14	11.6
33.50	4.4
33.90	6.3
34.30	5.6
34.56	7.9
34.76	5.1
38.87	6.3
36.12	5.9
36.32	6.3
37.28	8.0
37.89	5.9
38.19	9.6
38.75	8.1
39.41	5.2
39.86	9.2

The organic solvent forming the adducts in the above examples can be removed by drying or by using a displacing agent to produce further novel crystalline forms of the organic compound which improve its properties as a pharmaceutical agent.

Claims

1. An organic compound in a solid crystalline form that affords the compound improved handling properties and/or improved properties as a pharmaceutical agent.
5
2. An organic compound as claimed in claim 1, wherein said crystalline form is particulate and comprises substantially regularly shaped and free flowing crystalline particles.
10
3. An organic compound as claimed in claim 1 or claim 2, wherein said crystalline form is substantially free of water.
- 15 4. An organic compound as claimed in claim 1, 2 or 3 in the form of an adduct with an organic solvent.
5. An organic compound as claimed in an of claim 4, wherein the organic solvent is a polar organic solvent and is optionally miscible with water.
20
6. An organic compound as claimed in claim 4 or claim 5, wherein the organic solvent is dipolar and/or aprotic.
7. An organic compound as claimed in any of claims 4 - 6, wherein said organic compound is soluble in the organic solvent but substantially less soluble or insoluble in water.
25
8. An organic compound as claimed in any of claims 4 - 7, wherein the organic solvent is dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA) or 1-methyl-2-pyrrolidone (NMP).
30

9. An organic compound as claimed in any of claims 4–8, wherein the adduct includes the organic compound and the organic solvent in a 1:1 ratio.

10. An organic compound as claimed in any of claims 4–9, wherein the adduct has a crystal structure that includes a regular array of solvent and organic compound molecules.

11. An organic compound as claimed in any of claims 4–10, wherein the organic solvent comprises a plurality or mixture of solvent compounds.

12. An organic compound as claimed in any preceding claim, wherein said compound is Celecoxib, Rofecoxib, Olanzapine, Zafirlukast, Ondansetron, Clopidogrel, Ticlopidine, or a pharmaceutically acceptable salt or ester thereof.

13. An organic compound as claimed in claim 12, wherein said compound is Celecoxib.

14. An organic compound as claimed in any preceding claim, preparable or prepared by a method comprising precipitating said form or adduct from a solution of the organic compound in the organic solvent by the addition of water to the solution.

15. An organic compound as claimed in claim 14, wherein said method also comprises the step of drying the precipitated form or adduct to provide a crystalline form of the organic compound as claimed in any preceding claim.

16. An organic compound as claimed in claim 15, wherein the drying step involves conventional vacuum drying, optionally at a vacuum of down to 50, 40, 35, 30, 25 or 20 mm Hg and at a temperature of up to 20, 25, 35, 40, 45, 50, 55, 60°C.

17. An organic compound as claimed in any of claims 3–16, wherein the adduct is a solvate in which the solvent is bound into the crystal lattice of the organic compound.

18. A crystalline organic compound as claimed in claim 13 which is a 1:1 adduct of Celecoxib and DMA.
- 5 19. A crystalline organic compound as claimed in claim 13 which is a 1:1 adduct of Celecoxib and DMSO.
20. A crystalline organic compound as claimed in claim 13 which is a 1:1 adduct of Celecoxib and NMP.
- 10 21. A crystalline organic compound as claimed in claim 18 which is characterised by the X-ray data specified in Table 2.
22. A crystalline organic compound as claimed in claim 19 which is characterised
15 by the X-ray data specified in Table 3.
23. A crystalline organic compound as claimed in claim 20 which is characterised by the X-ray data specified in Table 4.
- 20 24. A process for preparing an organic compound as claimed in any of claims 1 – 23, comprising precipitating said compound from a solution of the organic compound in an organic solvent by the addition of water to the solution.
- 25 25. A process as claimed in claim 24, further comprising a step of drying the precipitate.
26. A process as claimed in claim 25, wherein the drying step involves conventional vacuum drying, optionally at a vacuum of down to 50, 40, 35, 30, 25 or 20 mm Hg and at a temperature of up to 20, 25, 35, 40, 45, 50, 55, 60°C.
- 30 27. A process as claimed in claim 24, 25 or 26, wherein the organic solvent, is a polar organic solvent that is optionally miscible with water.

28. A process as claimed in any of claims 24– 27 wherein the organic solvent is dipolar and/or aprotic.

29. A process as claimed in any of claims 24– 28 wherein the organic compound
5 is soluble in the organic solvent but substantially less soluble or insoluble in water.

30. A process as claimed in any of claims 24– 29, wherein the organic solvent is dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA) or 1-methyl-2-pyrrolidone (NMP).

31. A process as claimed in any of claims 24 – 30, wherein the organic
10 compound forms an adduct with the organic solvent.

32. A process as claimed in any of claims 24 – 31, wherein the organic solvent
15 comprises a plurality or mixture of solvent compounds.

33. A process as claimed in claim 31 or 33, wherein the organic compound is in the form of an adduct as defined in any of claims 4 – 23 and the organic solvent(s) in said adduct is provided from the solution.

34. A method for preparing an organic compound as claimed in claim 1 or claim 2 that is substantially free of organic solvent, comprising removing a substantial portion of the solvent(s) from an organic compound as claimed in any one of claims 4 - 23 that is in the form of an adduct as defined in any one of claims 4 - 23.

35. An organic compound, prepared or preparable by a method as claimed in claim 34.

36. An organic compound, prepared or preparable by a process as claimed in any
30 of claims 24 – 33.

37. A method of preparing a pharmaceutical dosage form utilising an organic compound as claimed in any of claims 1 – 23, 35 and 36.

38. A pharmaceutical dosage form prepared or preparable by a method as claimed in claim 37.

5 39. A pharmaceutical dosage form, comprising an organic compound as claimed in any of claims 1 – 23, 35 and 36 and at least one pharmaceutically acceptable excipient.

10 40. Use of an organic compound as claimed in any of claims 1 – 23, 35 and 36, for the preparation of a medicament for the therapeutic treatment of a human or animal body.

41. A use as claimed in claim 40, wherein the organic compound is Celecoxib, and the medicament is for treating osteoarthritis or rheumatoid arthritis.

15

42. A Celecoxib adduct, comprising Celecoxib and an organic solvent, in a solid crystalline form.

20 43. A method of preparing a pharmaceutical dosage form utilising a Celecoxib adduct as claimed in claim 42.

44. A pharmaceutical dosage form prepared or preparable by a method as claimed in claim 43.

25 45. A pharmaceutical dosage form, comprising a Celecoxib adduct as claimed in claim 42 and at least one pharmaceutically acceptable excipient.

46. Use of a Celecoxib adduct as claimed in claim 42 for the preparation of a medicament for treating osteoarthritis or rheumatoid arthritis.

30

FIG. 1

A scanning electron microscope image of Celecoxib crystals produced by conventional crystallisation techniques.

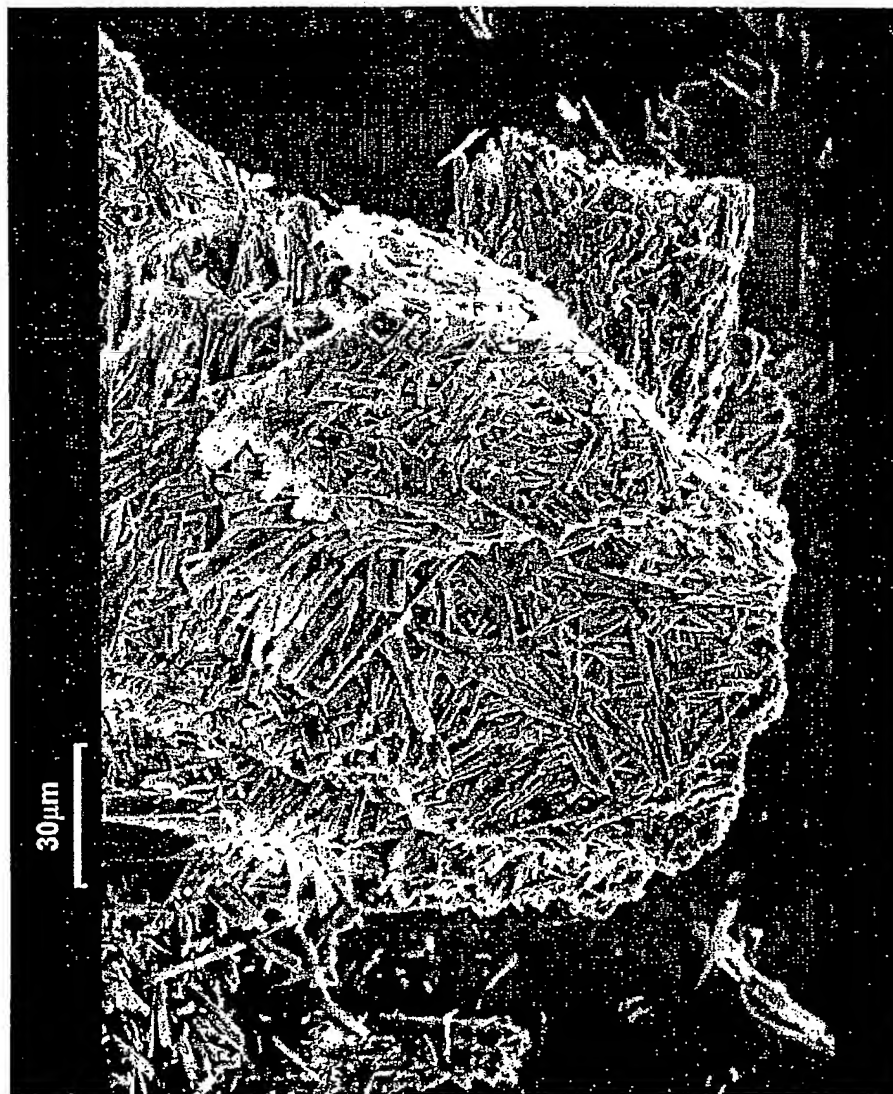


FIG. 2

A scanning selection microscope image of the Celecoxib-DMA adduct prepared in example 1.

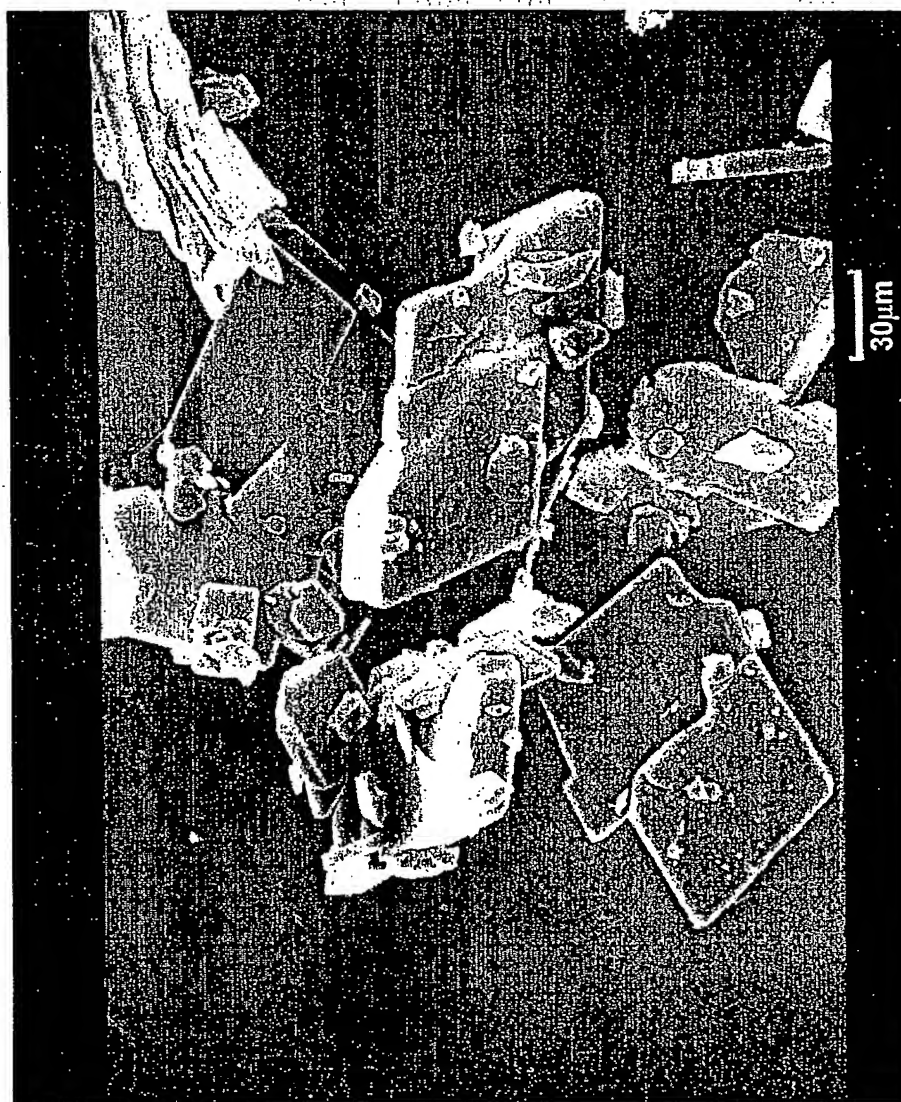


FIG. 3

A scanning electron microscope image of the Celecoxib:
DMSO adduct prepared in example 2.

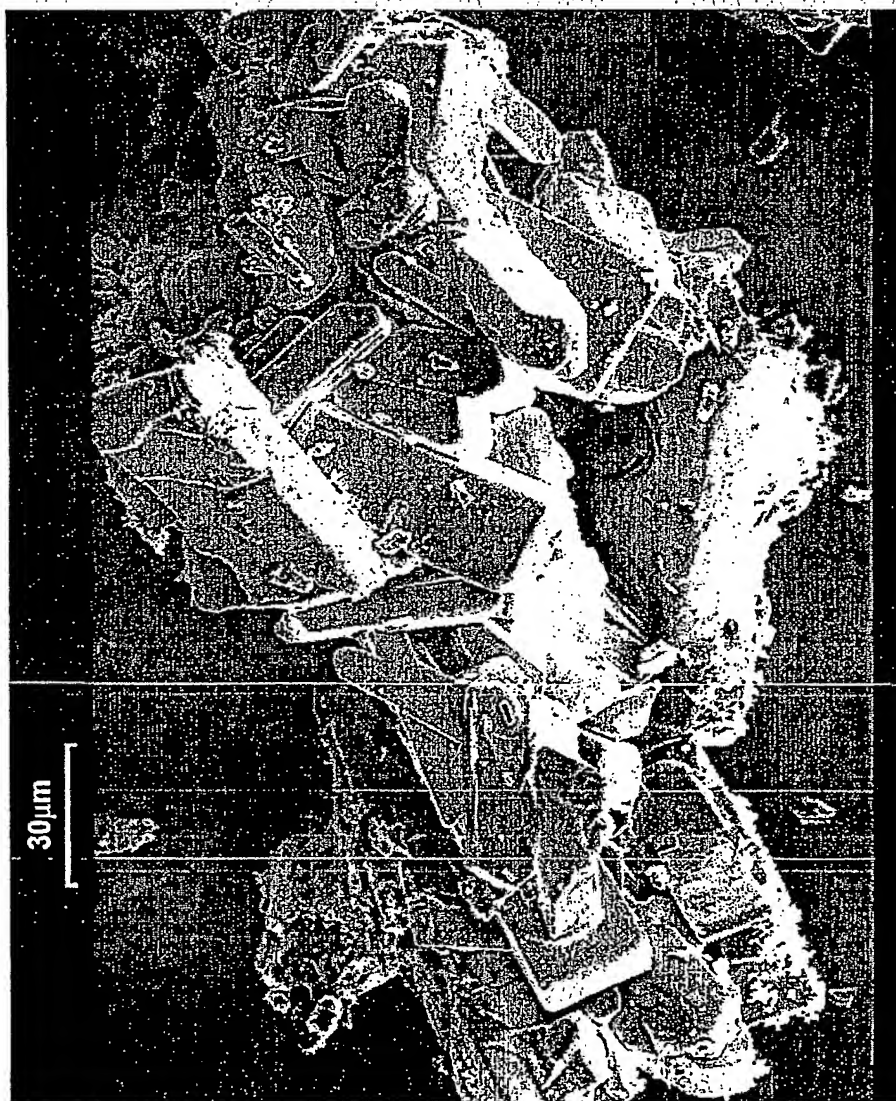
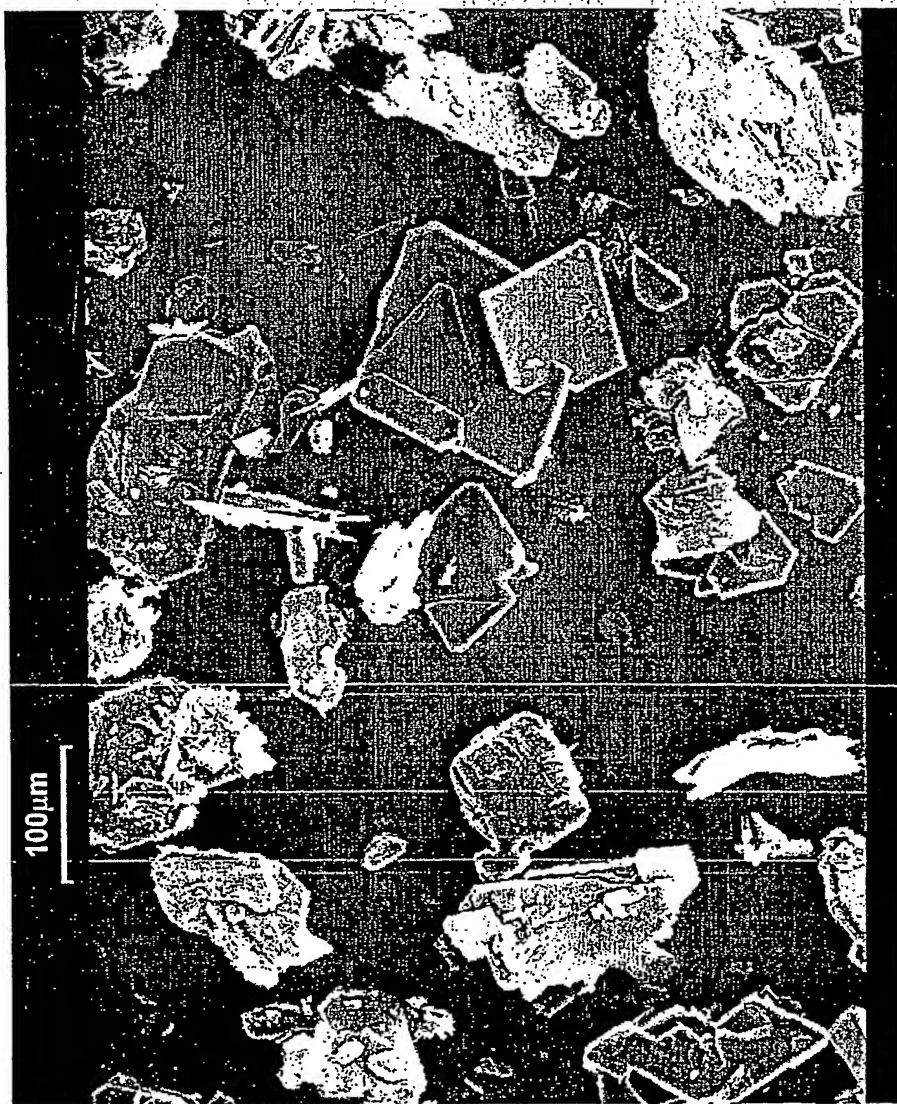


FIG. 4

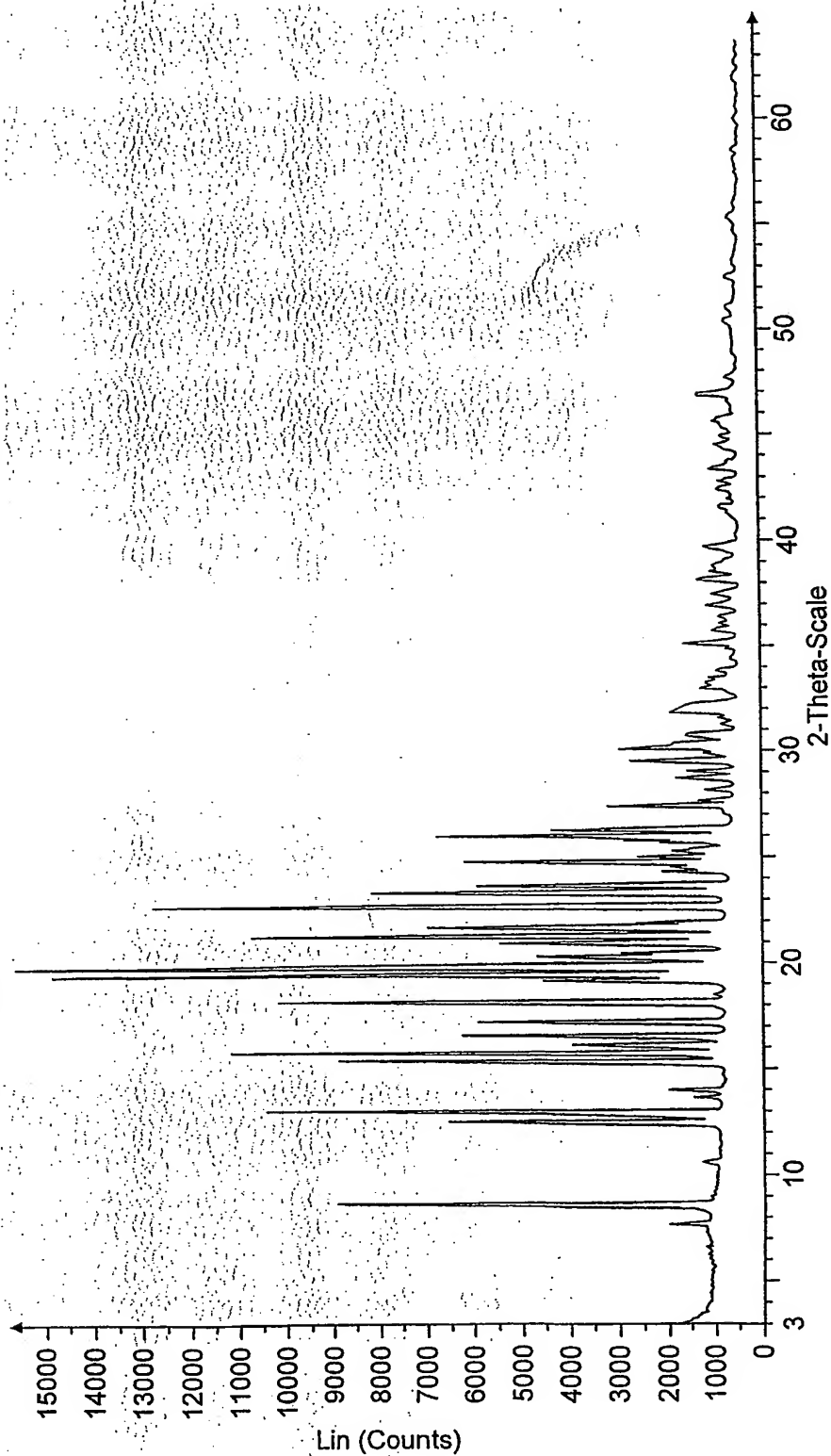
A scanning electron microscope image of the Celecoxib:
NMP adduct prepared in example 3.



5/12

FIG. 5

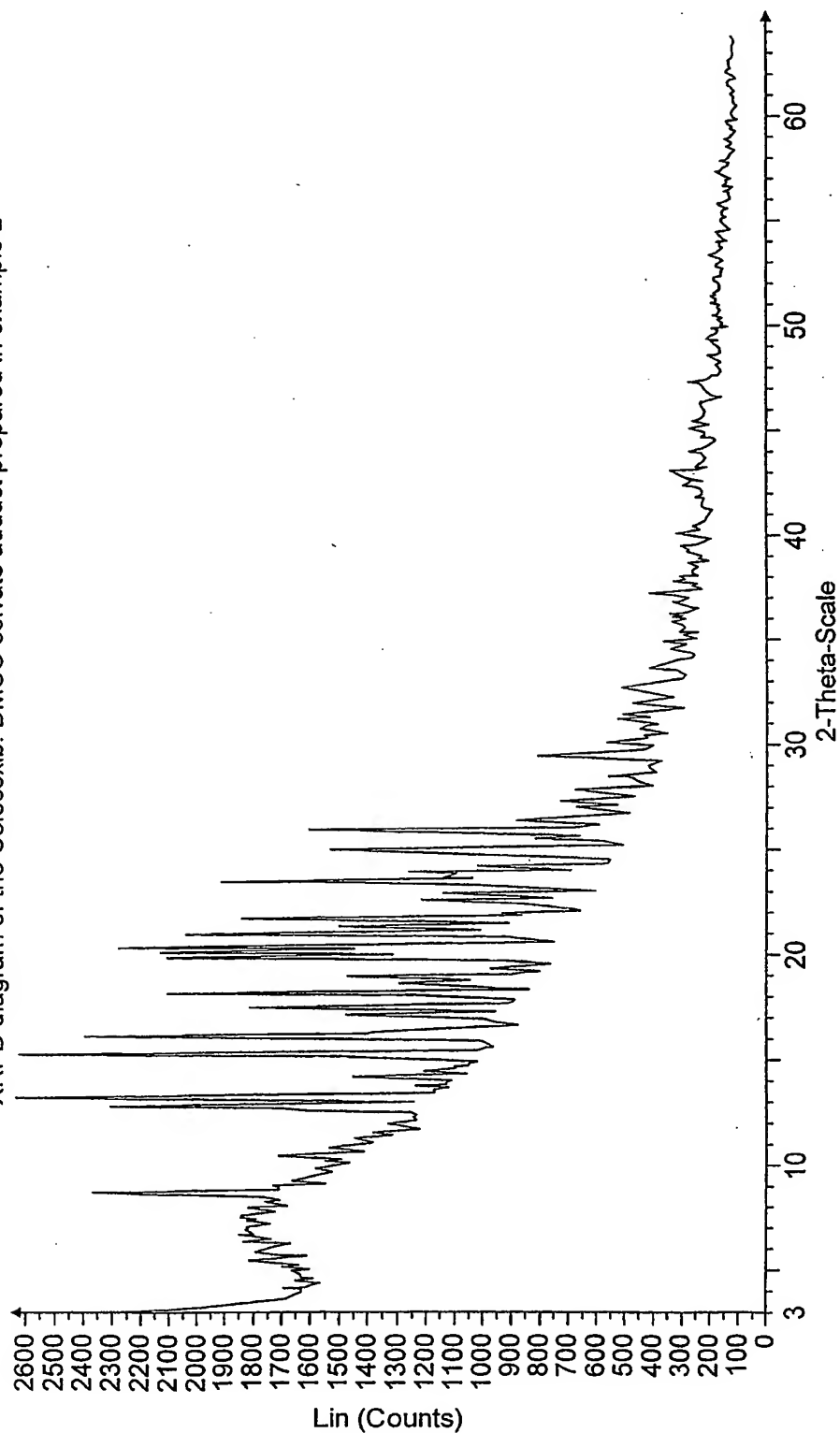
XRPD diagram of the Celecoxib: DMA solvate adduct prepared in example 1



6 / 12

FIG. 6

XRPD diagram of the Celecoxib: DMSO solvate adduct prepared in example 2

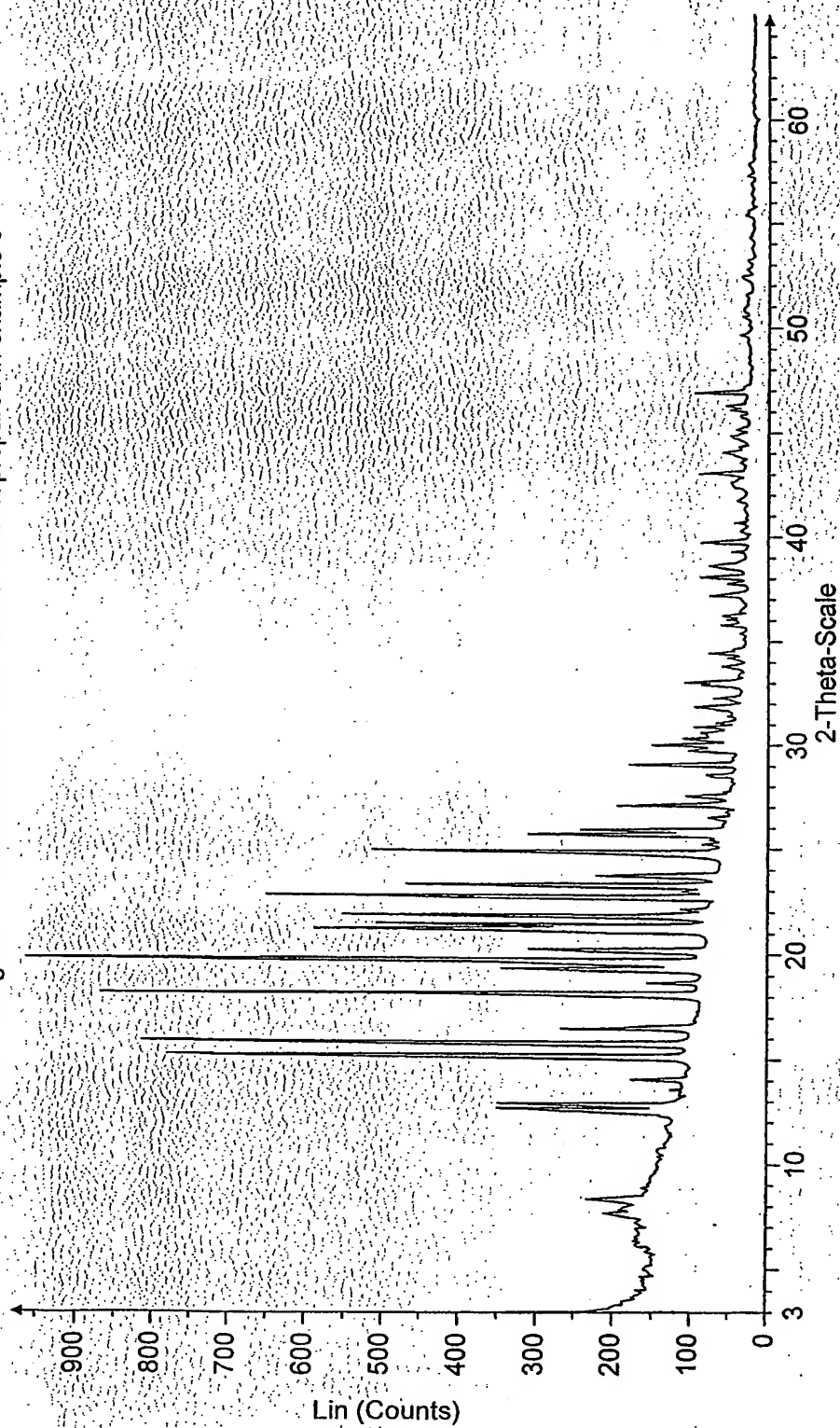


SUBSTITUTE SHEET (RULE 26)

7/12

FIG. 7

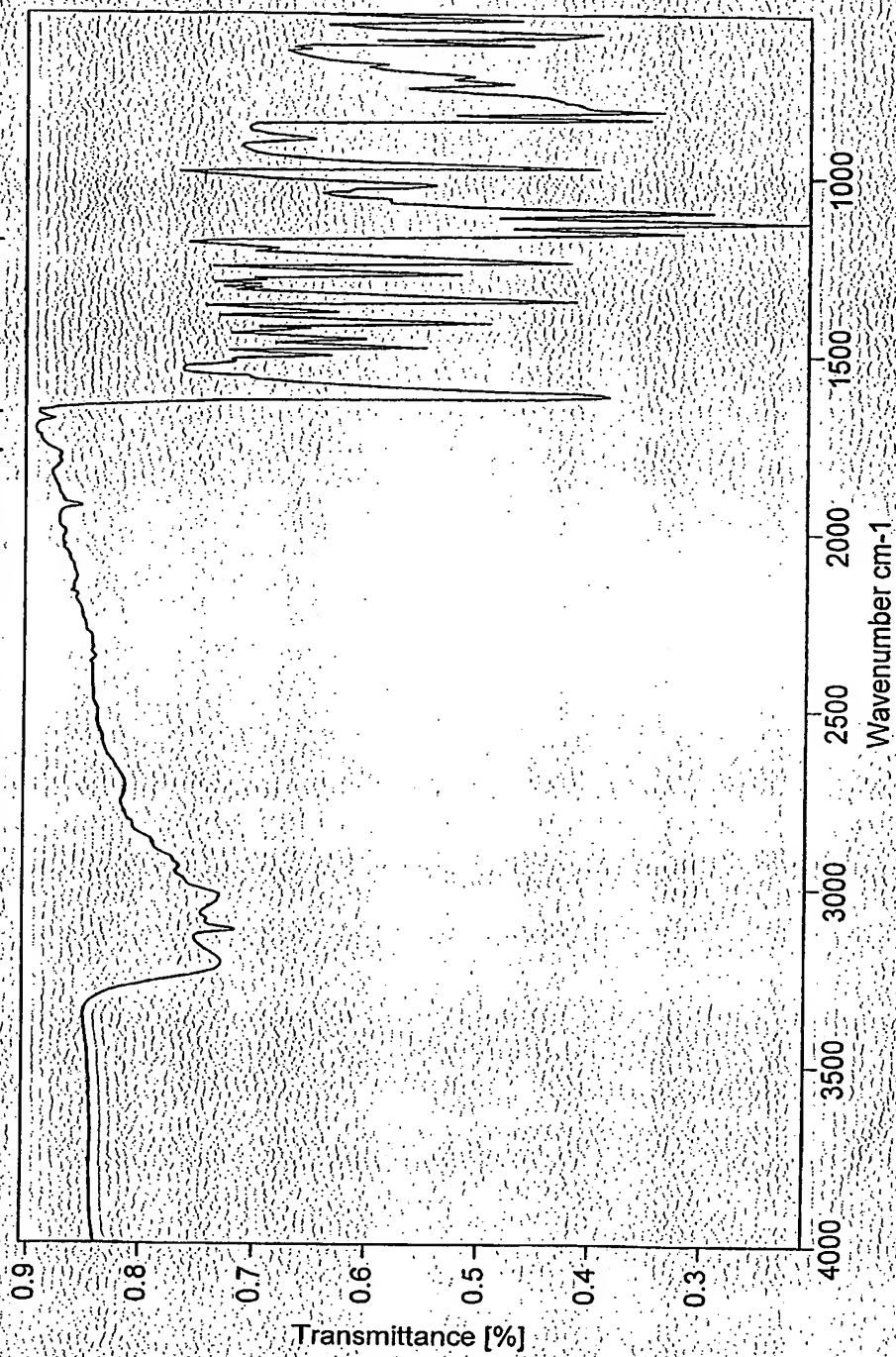
XRPD diagram of the Celecoxib-NMP solvate adduct prepared in example 3



8 / 12

FIG. 8

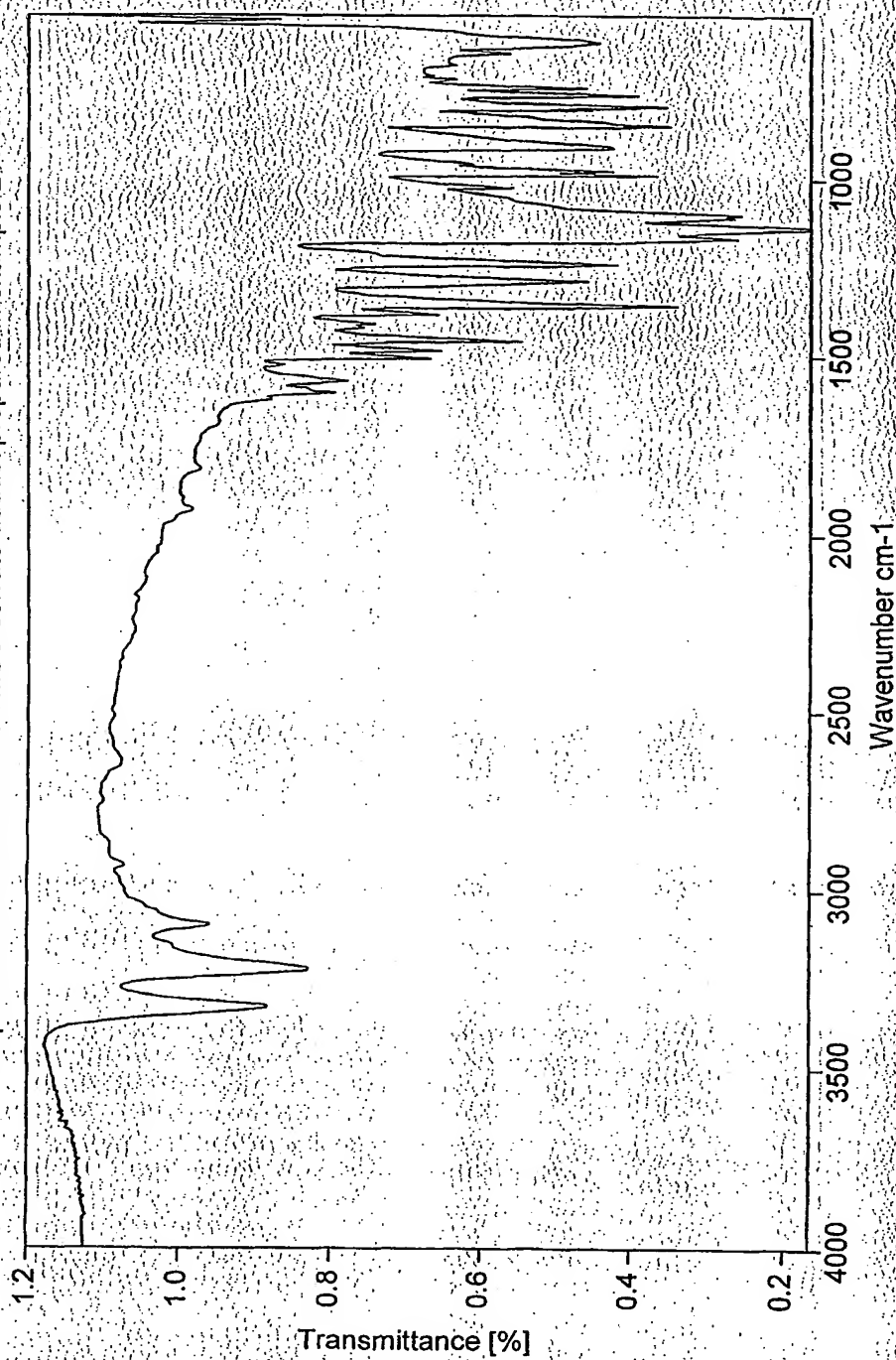
IR spectrum of the Celecoxib: DMA solvate adduct prepared in example 1



9/12

FIG. 9

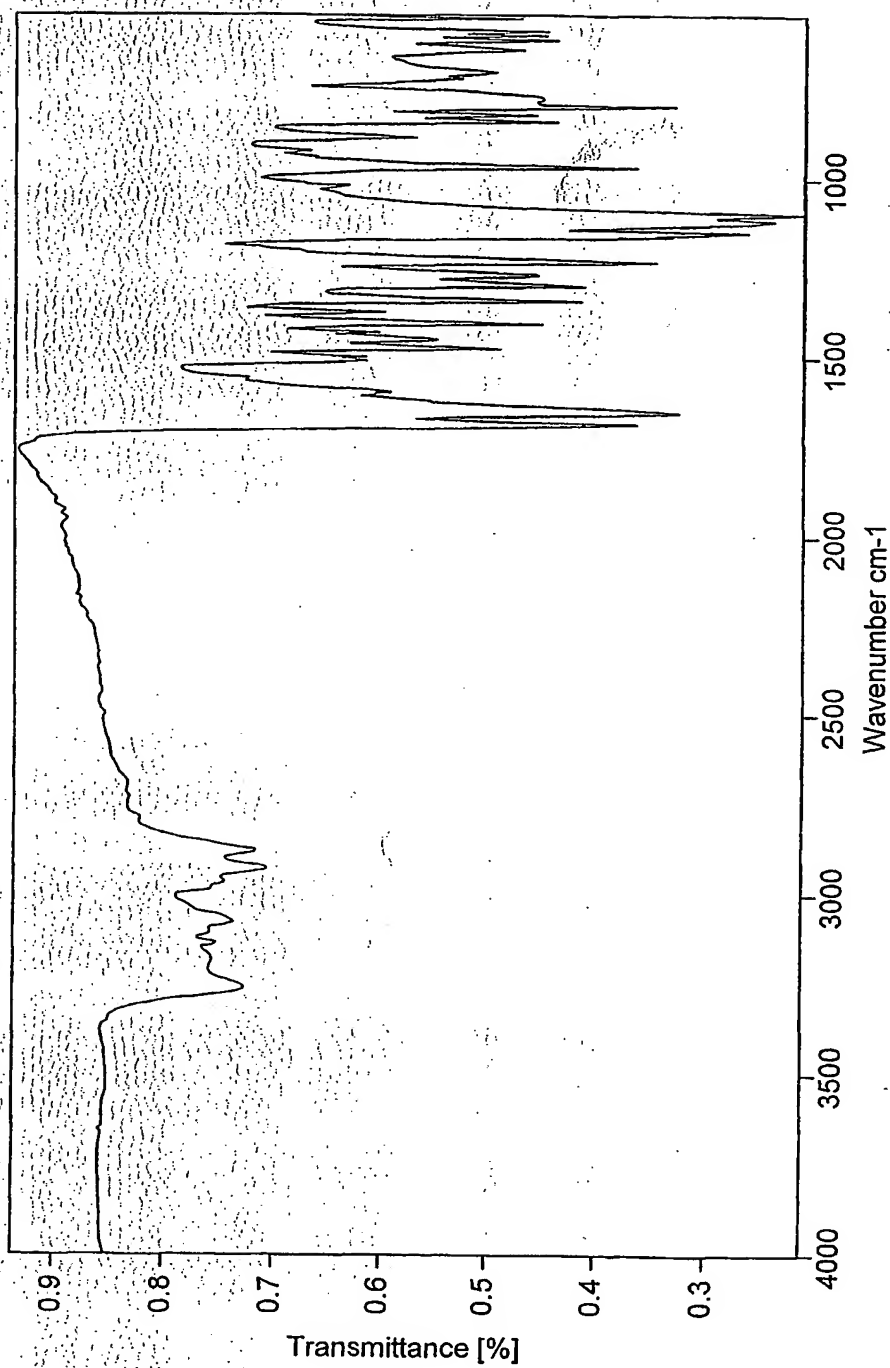
IR spectrum of the Celecoxib: DMSO solvate adduct prepared in example 2



10 / 12

FIG. 10

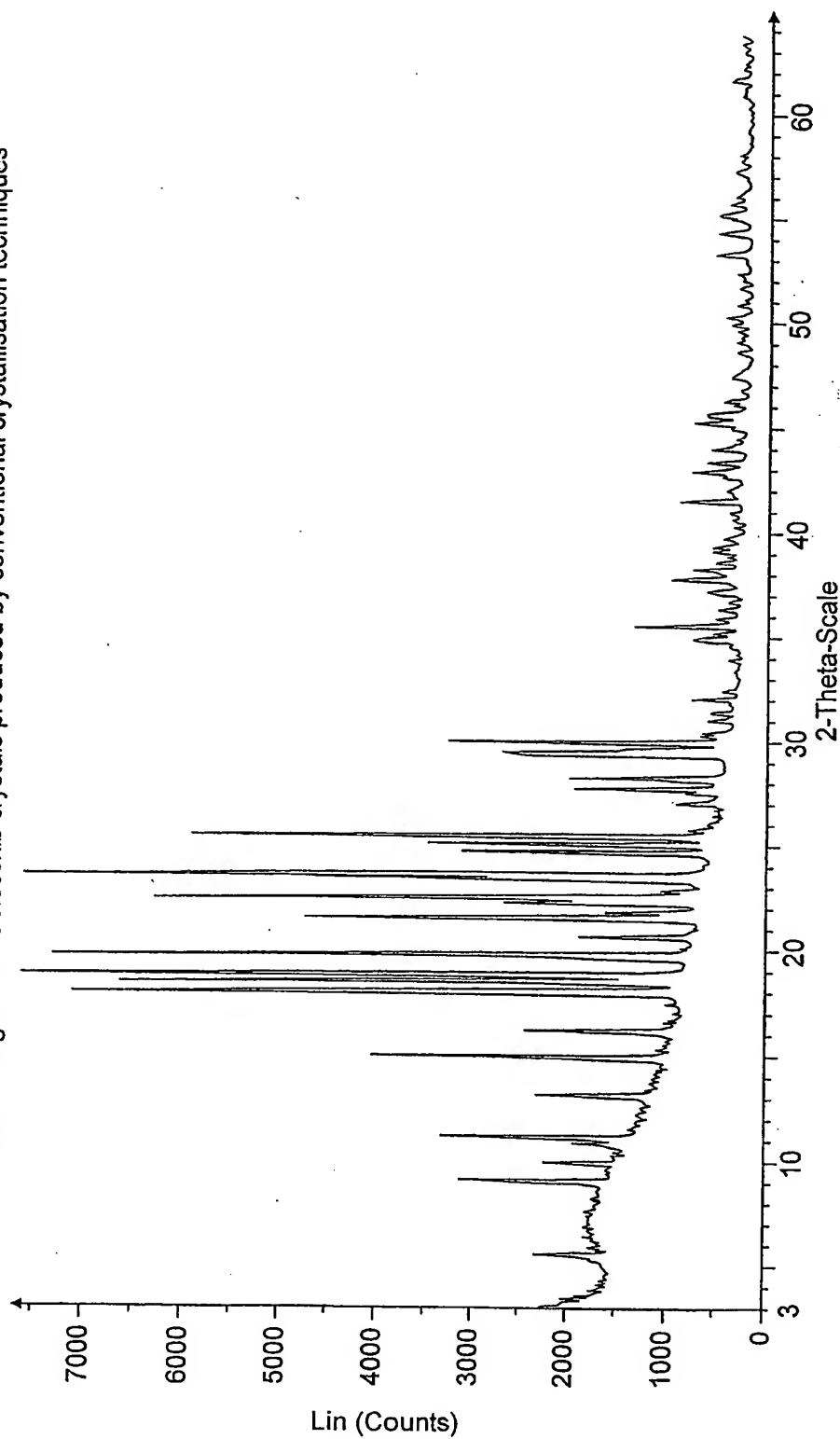
IR spectrum of the Celecoxib: NMP solvate adduct prepared in example 3



11 / 12

FIG. 11

XRPD diagram of Celecoxib crystals produced by conventional crystallisation techniques

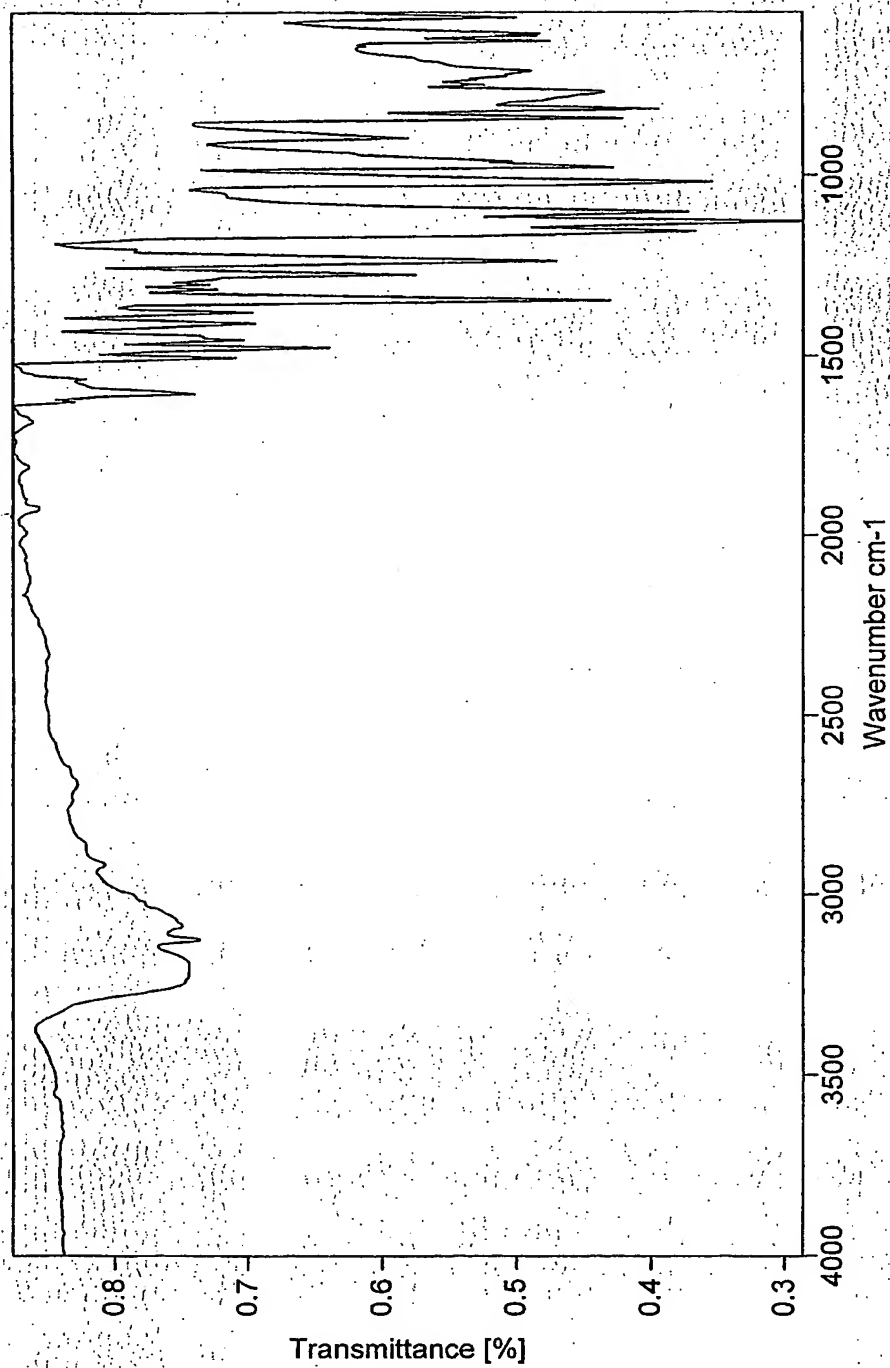


SUBSTITUTE SHEET (RULE 26)

12 / 12

FIG. 12

IR spectrum of Celecoxib crystals produced by conventional crystallisation techniques



INTERNATIONAL SEARCH REPORT

International Application No.
PC1/GB 02/01902

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K31/415 A61K31/4178 A61K31/404 A61K31/5513
A61K31/4365 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 00627 A (FAKO ILACLARI A S ;BAHAR MEHMET (TR); GOKTEPE MEHMET (TR); GUNDUZ) 3 January 2002 (2002-01-03) page 1, line 1-5 page 2, line 8-27 page 7, line 7-12 page 7, line 24 -page 8, line 13	1-18, 21-46
Y	claims 1-11	1-46
X	WO 01 42222 A (MIYAKE PATRICIA J ;FERRO LEONARD J (IL); PHARMACIA CORP (US)) 14 June 2001 (2001-06-14)	1-15, 17-19, 21-25, 27-46
Y	claim 66 page 60, line 11 -page 61, line 12	1-46
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

10 December 2002

Date of mailing of the international search report

30/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

Int'l Application No
Pc1/GB 02/01902

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 200143 Derwent Publications Ltd., London, GB; Class B05, AN 2001-398913 XP002224414 & CN 1 287 119 A (GUANGZHOU CHEM INST ACAD SINICA), 14 March 2001 (2001-03-14) abstract	1-7, 9-13, 17, 34-46
X	WO 02 18390 A (CHAKKA RAMESH ; REDDY S LAB LTD DR (IN); REGURI BUCHI REDDY (IN); K) 7 March 2002 (2002-03-07)	1, 2, 5-12, 14-17, 24-40
Y	claims 1-21	1-46
E	WO 02 38545 A (NISNEVICH GENNADY ; GUTMAN ARIE (IL); ZALTZMAN IGOR (IL); PERTSIKOV) 16 May 2002 (2002-05-16) claims 1-21	1-7, 9-12, 14-17, 24-29, 31-40

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 02/01902

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-11, 14-17 and 24-40 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds defined in claim 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 02/01902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0200627	A	03-01-2002	TR 200001872 A2 21-01-2002
		AU 7680801 A 08-01-2002	
		EP 1167355 A1 02-01-2002	
		WO 0200627 A1 03-01-2002	
		US 2002016351 A1 07-02-2002	
WO 0142222	A	14-06-2001	AU 1805901 A 18-06-2001
		AU 1930301 A 18-06-2001	
		AU 1931001 A 18-06-2001	
		AU 1931101 A 18-06-2001	
		AU 2041201 A 18-06-2001	
		AU 750978 B2 01-08-2002	
		AU 2057101 A 18-06-2001	
		BG 5808 A 30-09-2002	
		BG 105873 A 30-04-2002	
		BR 0008058 A 26-03-2002	
		BR 0008059 A 26-03-2002	
		BR 0008060 A 05-02-2002	
		BR 0008088 A 09-04-2002	
		CN 1376146 T 23-10-2002	
		CN 1379669 T 13-11-2002	
		CZ 20012875 A3 13-02-2002	
		CZ 20013162 A3 12-06-2002	
		CZ 20013163 A3 12-06-2002	
		CZ 20013210 A3 13-03-2002	
		EP 1175214 A2 30-01-2002	
		EP 1165072 A2 02-01-2002	
		EP 1150959 A1 07-11-2001	
		EP 1150960 A1 07-11-2001	
		HR 20010582 A1 31-08-2002	
		HR 20010589 A1 31-08-2002	
		HU 0200409 A2 29-06-2002	
		HU 0200580 A2 28-11-2002	
		NO 20013855 A 05-10-2001	
		NO 20013858 A 08-10-2001	
		NO 20013859 A 08-10-2001	
		NO 20013868 A 03-10-2001	
		NZ 513960 A 28-09-2001	
		NZ 513963 A 28-09-2001	
		NZ 513964 A 28-09-2001	
		NZ 514059 A 28-09-2001	
		PL 349223 A1 01-07-2002	
		PL 349224 A1 01-07-2002	
		SK 11522001 A3 09-05-2002	
		SK 12672001 A3 04-04-2002	
		SK 12682001 A3 02-07-2002	
		SK 12692001 A3 04-04-2002	
		TR 200102297 T1 21-03-2002	
		WO 0141536 A2 14-06-2001	
		WO 0141761 A2 14-06-2001	
		WO 0141762 A2 14-06-2001	
		WO 0141760 A2 14-06-2001	
		WO 0142221 A1 14-06-2001	
		WO 0142222 A1 14-06-2001	
		US 2002142045 A1 03-10-2002	
		US 2002006951 A1 17-01-2002	
CN 1287119	A	14-03-2001	NONE

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 02/01902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0218390 A	07-03-2002	AU 4347501 A WO 0218390 A1	13-03-2002 07-03-2002
WO 0238545 A	16-05-2002	AU 1265902 A WO 0238545 A2	21-05-2002 16-05-2002

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☒ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKewed/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☒ **GRAY SCALE DOCUMENTS**

☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.